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Prothrombin complex concentrate in cardiac surgery for the treatment of non-surgical bleeding (Protocol)

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[Intervention Protocol]

Prothrombin complex concentrate in cardiac surgery for the treatment of non-surgical bleeding

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of prothrombin complex concentrate in people undergoing cardiac surgery who have coagulopathic non-surgical bleeding

BACKGROUND

Description of the condition

Cardiac surgery is known to be associated with high blood product transfusion requirements and in turn allogenic blood transfusion is associated with higher rates of morbidity and mortality (Arias-Morales 2017; Kilic 2014). In 2016, it was estimated that one million people throughout the world undergo cardiac surgery each year (Veluz 2017). This number is only likely to increase with our aging population. In the UK, there are 30,000 cardiac procedures performed each year and it is estimated that 30% of these require plasma transfusion for bleeding and management of coagulopathy (Bortolussi 2019; Green 2019).

There is considerable risk of postoperative bleeding due to contact activation with the extracorporeal circulation system, factor degradation, platelet dysfunction and activation, fibrinogen consumption, reduced liver production of factors, foreign graft material, multiple suture lines, and raw open vascular surfaces (Achneck 2010).

Platelets may become activated but injury to these platelets may occur due to the shear forces of the cardiopulmonary bypass circuit and pump leading to impaired function. At the surgical site, blood is exposed to air and tissue factor, further activating coagulation cascade. These processes will ultimately result in consumption of coagulation factors, platelets, and fibrinogen, as well as increased fibrinolysis (O'Carroll-Kuehn 2007). A non-systematic search and review of the coagulation changes post-cardiopulmonary bypass showed that plasma fibrinogen concentration decreases during cardiopulmonary bypass with a median reduction of 36% with platelet count decreasing by 44% (Höfer 2016). They also showed that coagulation factors had an overall decrease in activity during cardiopulmonary bypass with factors II, V, VII, X, XI, and XIII all strongly decreased by an average of 47.0%, 39.9%, 23.5%, 40.3%, 35.6%, and 33.6%, respectively (Höfer 2016). An animal study looking at swine, showed that following cardiopulmonary bypass for two hours at 25 degrees celsius there was a fall of coagulation factors II, VII, IX and X up to 48% (Kaspereit 2010). It is hypothesised that these factors exponentially decrease the longer the patient is on cardiopulmonary bypass and the lower the temperature.

Description of the intervention

Prothrombin complex concentrate (PCC) includes both 4-factor concentrates (coagulation factors II, VII, IX, X) and 3-factor concentrates (coagulation factors II, IX, X). In Europe and Canada the 4-factor concentrate is predominantly used, for example Beriplex and Octaplex, whereas in Australia and New Zealand the only preparation available is the 3-factor concentrate e.g. Prothrombinex. (Sørensen 2011).

In the UK, factor concentrates became popular for treatment of haemophillia in the 1990s due to infectious risks associated with fresh frozen plasma (FFP) and cryoprecipitate (Köhler 1999). On a global scale, in 2017, EACTS/EACTA (European Association for Cardio-Thoracic Surgery/European Association of Cardiothoracic Anaesthesiology) taskforce published a comprehensive patient blood management guideline. They have recommended the use of PCC for coagulation factor deficiency in the treatment of microvascular bleeding but do not give a recommended dose or timing (Pagano 2018). Following on from this, in 2019, the American Society of Cardiovascular Anaesthesiologists have now included the use of low-dose PCC in their perioperative blood management guideline as an alternative to FFP however this treatment is recommended with caution as there is still uncertainty about dosing and side effects (Raphael 2019).

PCC comes with a potential prothrombic risk, given it is a low-volume, high-concentration of coagulation factors infused directly into the systemic circulation (Song 2014). 3-factor concentrates do not have protein S and C, therefore can add to the potential risk of thrombosis. Thrombosis has been described as cerebrovascular events, myocardial infarction, pulmonary embolisim and deep vein thrombosis (Franchini 2010). In a subset of patients with a prior history of deep vein thrombosis or pulmonary embolisims who were given 3-factor PCC for reversal of warfarin in the setting of intracerebral haemorrhage, there was a 4.5 times increased risk of developing a venous thromboembolism within 30 days (Felton 2016). There has been one documented case study of massive thrombosis following PCC administration, of the superior vena cava to the pulmonary artery requiring reinstitution of cardiopulmonary bypass and thrombectomy (Koster 2014).

The true risk of acute kidney injury with PCC is unknown. Cappabiancca and his team showed an increased risk incidence of acute kidney injury and dialysis with PCC when compared to FFP (Cappabianca 2016). Subsequently there has been published data showing that there is no increased risk of acute kidney injury (Fitzgerald 2018; Harper 2018). The unknown is the use of PCC for bleeding in patients with mechanical support such as left ventricular assist devices and extracorporeal membrane oxygenation.

PCC has a low transfusion volume, (500-unit vial is reconstituted in 20 mL). The patient receives less overall fluid volume, which will potentially avoid volume overload of the right ventricle and reduce incidence of lung oedema. PCC is also not associated with transfusion-related acute lung injury. The advised rate of transfusion is 3 mL to 6 mL per minute or as tolerated by the patient (Product Information - Prothrombinex-VF, Pabinger 2010). PCC has a shelf life of six months at room temperature and will allow for immediate availability for factor replacement. Unlike other clotting factors, PCC does not require blood group specificity and has an improved safety profile (Tanaka 2010).

PCC is a sterile freeze-powder containing purified human coagulation factors. The concentrate is produced by ion-exchange chromatography from the cryoprecipitate of large plasma pools after removal of factor IX and antithrombin (Franchini 2010).

- The 3-factor PCC (eg. Prothrombinex-VF) is presented in 500 IU vials that contain 500 IU of factors II, IX and X, 25 IU of antithrombin 3, 192 IU of heparin and electrolyte buffers.
- The 4-factor PCC (eg. Beriplex) is presented in 500 IU vials that contain 380 to 800 IU of factor II, 200 to 500 IU of factor VII, 500 IU of factor IX, 500 to 1020 IU of factor X, 420 to 820 IU of protein C and 240 to 680 IU of protein S.

Intravenous administration means that the preparation is available immediately, and bioavailability is 100%. Patients who received a 50 IU/kg intravenous dose, showed that peak plasma concentrations of the coagulation factors occur within five minutes of infusion (Ostermann 2007).

PCC is distributed and metabolised in the same way as endogenous coagulation factors (Franchini 2010).

PCC administration is contraindicated in patients with known allergy to heparin or history of heparin-induced thrombocytopenia and with active thrombosis or disseminated intravascular coagulopathy. Heparin-induced thrombocytopenia is related to the low level of porcine heparin in some types of PCCs eg, Prothrombinex. There were no documented heparin-induced thrombocytopenias secondary to PCCs in a pharmacovigilance study of Beriplex from 1996 to 2012 (Hanke 2013). There are no known drug interactions with PCCs.

Elimination half-life of the coagulation factors is: factor II, 60 hours; factor VII, 4.2 hours; factor IX, 17 hours; and factor X, 31 hours (Franchini 2010).

How the intervention might work

The treatment of bleeding diathesis following cardiac surgery is a considerable challenge and has been traditionally based on transfusion of allogenic blood products (Kilic 2014). Typically a volume of 20 mL/kg of FFP is required to produce a 30% increase in factor levels (Nascimento 2010). Substantial volumes of FFP are required to ensure adequate factor replacement and as a consequence there can be dilution of other clotting constituents, including platelets, fibrinogen and red blood cells (Ishikura 2017; Nascimento 2010). PCC is currently used in the treatment and perioperative prophylaxis of acquired deficiency of prothrombin complex factors and bleeding in patients with congenital deficiency of individual coagulation factors when specific products are not available (Estrada 2016; Siddon 2016; Van Veen 2007). It is also used in the treatment of warfarin reversal prior to urgent or emergency surgery (Bordeleau 2015; Unold 2015; Van Veen 2007). Studies of PCC for warfarin reversal show that there is reversal of anticoagulation within 10 minutes following administration (Riess 2007), in comparison to FFP, which takes hours, and with which INR (International Normalised Ratio) correction can also be incomplete (Cartmill 2000). Furthermore FFP correction is also delayed due to prescription, cross-matching and administration time (Bordeleau 2015), and it is unable to correct an INR to less than 1.6 (Yazer 2010).

FFP contains all the coagulation factors except platelets. It is the fluid portion of a unit of whole blood that is frozen. FFP contains all coagulation factors and other plasma proteins (albumin), including fibrinogen (400 to 900 mg/unit), physiological anticoagulants (protein C and S, antithrombin and tissue factor pathway inhibitor). Following thawing of FFP, factors V and VIII have a gradual decline requiring re-administration if there is ongoing bleeding (Nascimento 2010).

In comparison, following administration of PCC there is correction of vitamin K-dependent coagulation factors II, VII, IX and X and antithrombotic proteins C and S (in 4-factor PCC). The 3-factor PCC contains only factors II, IX and X with generally small amounts of factor VII, antithrombin and small amounts of heparin. Following increase of these substrate coagulation proteins there is enhanced thrombin generation, which illustrates the ability of PCC to support the enzyme complexes that convert factor II to IIa (Ghadimi 2016).

Factor II is converted to thrombin by the presence of activated factor X. Thrombin converts fibrinogen to fibrin to enhance clot formation. Factor VII is converted to VIIa and binds to tissue factor, which then activates factor IX and the primary coagulation pathway. Factor IX in the presence of VIIIa activates factor X. Factor X is activated to convert prothrombin to thrombin in the presence of phospholipids and calcium ions. Protein C is activated by thrombin to then exert an antithrombotic effect, whereas protein S exists in a free form as a cofactor for activated protein C (Ghadimi 2016).

FFP has the advantage of containing all the required factors but in a dilute form, and large volumes are required for relatively small increments in factor levels. Conversely PCC increases the key factors to a much larger extent. PCC is the ideal reversal agent of warfarin as the depleted factors are the vitamin K-dependent ones.

Why it is important to do this review

Internationally there is a growing collection of hospital-based coagulation algorithms utilising PCC as factor replacement and as rescue therapy for the correction of coagulopathy post-cardiac surgery. These centres mentioned are using PCC with point-of-care testing with thromboelastography such as rotational thromboelastometry (ROTEM) and thromboelastography (TEG). Montreal Heart Institute published their coagulation algorithm utilising PCC with ROTEM guidance with a dose of 10-15 units/kg (Denault 2014). Duke University Hospital have recently published their algorithm (Hashmi 2019). Prince Charles hospital in Brisbane have also published an algorithm in association with National Blood Authority Australia (NBAA).

There are currently no randomised controlled trials (RCTs) in this area. There are, however, two trials listed on clinicaltrials.gov. One is a pilot in a single centre in London comparing FFP to PCC for patients who are bleeding during cardiac surgery (Green 2019). The other is a Mayo Clinic trial based in Rochester, sponsored by CSL Behring, looking at PCC compared to FFP for post-cardiopulmonary bypass coagulopathy and bleeding (Roman 2019). This second study utilises laboratory testing and not point-of-care coagulation testing.

There is one publication stating it is a “Systematic Review and Meta-Analysis”, published in 2019, where it identified four studies to analyse with a total of 861 adult participants, none of these were randomised. The four studies the authors included were all retrospective cohorts.The authors concluded that PCC appeared to be more effective than FFP in reducing perioperative blood transfusions and with no additional risk of thromboembolic events (Roman 2019). The studies identified only included the one comparator, which was FFP and it was limited to adults. In this growing area of research there are additional studies that need to be included.

This review would be the first step in summarising the entire literature in order to perform a comprehensive study that will assist in coagulation management and lead on to creating an international guideline. We believe that with the introduction of PCC there should be robust literature to support its use. PCC is potentially a very effective treatment option, which may reduce incidence of organ dysfunction, reduce blood transfusion and postoperative bleeding. It is cost-effective but its safety and side effects need to be established before this becomes standard treatment worldwide.

OBJECTIVES

To assess the benefits and harms of prothrombin complex concentrate in people undergoing cardiac surgery who have coagulopathic non-surgical bleeding

METHODS

Criteria for considering studies for this review

Types of studies

We will include individual randomised controlled trials (RCTs) if they exist, with both blinded and unblinded assessment of outcome. We will not include cluster- and cross-over RCTs. Due to the low incidence of patients that could potentially benefit, this treatment is more likely to be studied in non-randomised studies.

In conjunction with these studies we will also include non-randomised trials: cohort trials, both prospective and retrospective in design; case-control studies, as this is a reasonable study design to use, due to the rarity of the patients undergoing this procedure; and before and after studies, as the research may have occurred when hospitals changed their guidelines or policies. As this treatment is already in practice, it is important to summarise the current available evidence. Studies must analyse our described intervention and if possible, compare with FFP or recombinant factor VIIa, or both.

For the non-randomised studies, we have chosen the most robust designs that we believe we will be able to answer the question of interest with minimal risk of bias. We will not exclude studies on the basis of language of publication or publication status. We will exclude animal studies and non-clinical trials (in-vitro, ex-vivo, in-vivo and in-silico).

We will include case reports, which include outcomes on adverse events.

Types of participants

We will include studies with participants of all age groups undergoing cardiac surgery who had non-surgical bleeding (coagulopathy post-cardiopulmonary bypass).

We will exclude studies that use PCC for reversal of warfarin or vitamin K antagonists, and preoperative haemorrhagic diathesis (for example, haemophilia A and B, myelodysplastic syndrome, von Willebrand disease, immune thrombocytopenic purpura).

We believe that part of the resultant coagulopathy is a consequence of cardiopulmonary bypass, consequently, we will exclude any off-pump cardiac surgery.

If we cannot separate participants from cardiac surgery and other forms surgery then we will write to the study authors to obtain data. From there, as long as 80% are cardiac patients, then we will include the data.

Types of interventions

We will include studies where PCC is prescribed for the intended purpose of factor replacement, as first-line or rescue therapy (last-resort therapy for refractory bleeding), or both, to reduce non-surgical bleeding. There are many forms of PCC available internationally and we will be reviewing both 3- and 4-factor products (Appendix 1). We will exclude single-factor concentrates labelled 'prothrombin complex concentrates'.

Comparators will include standard therapy (current institutional protocol for bleeding diathesis), FFP and recombinant factor VIIa.

We will include studies that used PCC as monotherapy but not that used it in combination with either of the comparators (delivery separately to contrast effect or together) for the same intended therapeutic effect (reduction in non-surgical bleeding). We will include studies with any described doses providing that they gave our intervention and comparators intravenously. We will exclude studies using or comparing activated PCC because it contains an activated form of factor VII and this will cause confounding since recombinant factor VIIa is one of our direct comparators.

A confounding factor is that patients that receive PCC are likely to be higher risk of perioperative mortality and coagulopathy. Factors that define high risk are defined further in the analysis section.

Types of outcome measures

Primary outcomes

1. Blood products transfused: defined as all products (whole blood, red blood cells, FFP, cryoprecipitate, platelets and fibrinogen concentrate) transfused in theatre and postoperatively, before and after, the intervention or comparator, within 24 hours (mLs)
2. Thrombotic events: defined as new venous and arterial thromboses within 30 days
3. Mortality: defined as all-cause mortality following cardiac surgery within 30 days

Secondary outcomes

1. Bleeding: reviewed by postoperative drain output in the intensive care unit. We will not use intraoperative blood loss as a primary outcome for bleeding because it is poorly mentioned in the literature following cardiac surgery. Drain output is defined as total blood loss from the mediastinal and pleural drains in the first 12 hours (mLs)
2. Intensive care unit length of stay: defined as the total stay in intensive care following surgery (hours)
3. Incidence of renal impairment: defined as new or acute renal impairment requiring temporary continuous renal replacement therapy or sustained low-efficiency daily diafiltration within 30 days
4. Ventilator hours: the duration of intubation while in the intensive care unit
5. Adverse events: any other adverse event reported within the primary studies not included in the above outcomes

Search methods for identification of studies

Electronic searches

We will search the following electronic databases to identify relevant studies:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
2. MEDLINE (Ovid, 1946 to current);
3. Embase (Ovid, 1980 to current);

4. Conference Proceedings Citation Index-Science (CPCI-S) on the Web of Science (Clarivate Analytics, 1990 to current).

We will search Clinicaltrials.gov (www.clinicaltrials.gov), and the World Health Organisation (WHO), International Clinical Trials Registry platform (ICTRP; apps.who.int/trialsearch/), for ongoing or unpublished trials.

We have developed specific search strategies for this review and specific terms for the interventions of interest and their combinations. The preliminary search strategy for MEDLINE is listed in (Appendix 2), this will be adapted for the other databases. There was production and use of PCC prior to 2000, however these PCCs are known to have different constituents and posed an increased thrombosis risk (Köhler 1999), therefore we have chosen to start the literature search from 2000. This is in relation to the European Medicines Authority (EMA) gaining regulatory approval in 2005 (European Medicine Authority).

We will impose no restriction on language of publication or publication status. We will not perform a separate search for adverse effects of interventions used for the treatment of coagulopathy post-cardiopulmonary bypass. We will consider adverse effects described in included studies only.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will also contact principal investigators of identified studies to ascertain if they are aware of any other relevant published or unpublished matching clinical studies.

Data collection and analysis

Selection of studies

Two review authors (KH and CF) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search using Covidence and code them as 'yes include' (eligible or potentially eligible/unclear) or 'do not include' or 'maybe' if full text required to clarify (Covidence). We will resolve any disagreements about abstract suitability by discussion and consensus. We will retrieve the full-text study reports or publication and two review authors (KH and CF) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or a third-party decision (VJ). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Two review authors (KH and MF) will extract study characteristics from included studies separately and then compare and resolve conflicts. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, and date of study. For cohort and case control studies we will collect information about where the control group was sourced. For the cohorts we will determine whether it is retrospective or prospective in design.
2. Participants: number randomised, number lost to follow-up or withdrawn, number analysed, mean age, age range, gender, inclusion criteria, and exclusion criteria. Cardiac-specific data that we will collect includes: type of cardiac surgery, duration of cardiopulmonary bypass, deep hypothermic arrest required, emergency surgery, pre-operative anticoagulants, redo surgery, and when available laboratory coagulation test results and point-of-care test results. Interventions: intervention, comparison and we would include any information regarding cointerventions, though we are not expecting any cointerventions at this stage.
3. Outcomes: primary and secondary outcomes specified and collected, and time points reported. We will also collect both adjusted and unadjusted data. When collecting the adjusted data we will note what variables data have been adjusted for.
4. Notes: funding for trial, and notable conflicts of interest of study authors.

Two review authors (KH, MF) will independently extract outcome data from included studies. We will resolve disagreements by consensus. One review author (KH) will transfer data into the Review Manager 5 (Review Manager 2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the data extraction form.

Assessment of risk of bias in included studies

Two review authors (KH and MF) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). For RCTs, we will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table for RCTs and in a supplementary table for non-RCTs. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a study author, we will note this in the 'Risk of bias' table.

For non RCTs we will use the ROBINS-I tool for assessing the bias (Sterne 2016). This tool shows substantial overlap with the risk of bias ratings in RCTs, but additionally includes two domains at the pre-intervention level (bias due to confounding, bias in selection of participants into the study), and one domain at the intervention level (bias in classification of interventions). This uses a five-point scale (low/moderate/serious/critical/unclear risk) for the assessment of bias in non-randomised studies of interventions

(NRSI). We will exclude NRSIs that are of critical risk of bias. The primary analysis will be limited to studies at a low to moderate risk of bias (Reeves 2019).

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

The most important confounding domains are those factors that increase the risk of bleeding. The factors affecting this are:

1. age over 75 years
2. active endocarditis
3. redo surgery
4. more than one cardiac surgical procedure

All of these factors are covered in the EuroSCORE II (Nashef 2012). However in addition to these EuroSCORE II factors, there are also these factors:

1. Use of deep hypothermic cardiopulmonary arrest
2. CBP more than 180 minutes
3. BMI less than 25
4. urgent/emergent
5. pre-operative anticoagulants
6. aortic surgical work
7. pre-operative anaemia
8. aortic valve disease (regurgitation/stenosis/both)
9. history of thrombosis or coagulation defect

Measures of treatment effect

Where possible, we will choose adjusted estimates over unadjusted. We will collect adjusted odds ratios (ORs) by preference, with 95% confidence interval (CI) from the NRSIs and if adjusted data are not available we will collect unadjusted ORs with 95% CI. If adjusted data are supplied by the NRSIs we will analyse these using generic inverse variance by using log ORs and standard errors. We will note adjustments made by the individual studies within the footnote section of the forest plot.

We will analyse continuous data as mean difference (MD) with 95% CI. We will enter data presented as a scale with a consistent direction of effect. We will measure dichotomous data with risk ratios (RRs).

If data are not supplied in a form that is appropriate for meta analysis we will display results in a table format.

We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

Cross-over studies and cluster-RCTs are not included. For the outcomes where information may be described as an overall, that is, number of units of blood transfused and hours of hospital stay, we will extract these as mean numbers per person to avoid unit of analysis issues.

In a multi-arm study, we will divide the control group in order to ensure that no controls are double counted.

For multiple time points we will use the outcome that is closest to the prespecified outcome measure. For NRSIs, if multiple adjusted estimates are reported, we will choose the one that is judged to minimise the risk of bias due to confounding.

Dealing with missing data

We will contact study authors or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when we identify a study that is only available as an abstract). Where possible, we will use the Review Manager 5 (Review Manager 2014), calculator to calculate missing standard deviations using other data from the study, such as confidence intervals, based on methods outlined in *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Where this is not possible, and we thank that the missing data would introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. We will address the potential impact of the missing data in our discussion.

Assessment of heterogeneity

Any variability among the studies in a systematic review may be caused by clinical, methodological or statistical heterogeneity. Any variability in the participants, interventions and outcomes studied will be described as clinical diversity and any variability in the study design and risk bias will be described as methodological diversity (Deeks 2019). Variability with the intervention effects studied is known as statistical heterogeneity (referred to simply as heterogeneity) and can be a consequence of clinical or methodological diversity, or both. This may result in the observed intervention effects being more different from each other than one would expect due to random error alone (Deeks 2019).

With the known lack of RCTs on the topic to be reviewed we may expect to see heterogeneity due to both clinical and methodological diversity.

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We will use the I^2 statistic (Higgins 2003), to measure heterogeneity among the studies in each analysis, but acknowledge that there is substantial uncertainty in the value of the I^2 statistic when there is only a small number of studies, so we will also consider the P value from the Chi^2 test.

If we identify substantial heterogeneity greater than 50% , we will report it and explore possible causes by prespecified subgroup analysis (Deeks 2019).

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study biases for the primary outcomes (Page 2019).

Data synthesis

We will carry out statistical analysis using Review Manager 5 (Review Manager 2014). We will undertake meta-analyses only where this is meaningful, that is, the treatments, participants and the underlying clinical questions are similar enough for pooling to make sense. We will use a random-effects model as we do anticipate heterogeneity in the participant or intervention

characteristics. We will carry out separate meta-analysis for RCTs and NRSIs.

We will analyse separately NRSIs with different study features.

If data are unavailable to be pooled, we will present them in a narrative summary with tables if appropriate.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table using the following outcomes.

1. Blood products transfused: defined as all products (whole blood, red blood cells, FFP, cryoprecipitate, platelets and fibrinogen concentrate) transfused in theatre and postoperatively before and after the intervention or comparator, or both, within 24 hours.
2. Thrombotic events: defined as new venous and arterial thromboses within 30 days
3. Mortality: defined as all-cause mortality following cardiac surgery in patients who received the intervention or comparator within 30 days.
4. Bleeding: reviewed by postoperative drain output in the intensive care unit. We will not use intraoperative blood loss as a primary outcome for bleeding because it is poorly mentioned in the literature following cardiac surgery. Drain output is defined as hourly blood loss from the mediastinal and pleural drains in the first 24 hours.
5. Intensive care unit length of stay: defined as the total stay in intensive care following surgery (hours)
6. Incidence of renal impairment is defined as new or acute renal impairment requiring temporary continuous renal replacement therapy or sustained low-efficiency daily diafiltration within 30 days
7. Adverse events: any other adverse event reported within the primary studies not included in the above outcomes

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019a) using GRADEpro software (GRADEpro GDT). We will create different 'Summary of findings' tables for RCTs and NRSIs.

We will have two comparators, FFP and recombinant factor VIIa and we will compare both of these to PCC. We will develop a separate 'Summary of findings' table for each comparison and we will analyse each comparison separately. We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid readers' understanding of the review where necessary.

Two review authors (KH and CF), will work independently to judge evidence quality, and will resolve any disagreements by discussion or by involving a third review author, VJ. We will justify and document our judgements, and incorporate them into reporting of results for each outcome. We will make our judgements in accordance with recommendations on how the ROBINS-I tool should integrate with GRADE. Evidence will start at high quality and will be downgraded according to the five domains that can lower certainty (Schünemann 2019b).

We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table before writing the results and conclusions of our review.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. High risk for coagulopathy versus low risk for coagulopathy. For the definition of high risk versus low risk we will rely on the definition of the primary studies.
2. Use of PCC for rescue treatment in refractory bleeding versus recombinant factor VIIa
3. Adult (>18 years) versus children (0-18 years)
4. Four factor PCC versus three factor PCC

We will use the formal test for subgroup differences in Review Manager 5 (Review Manager 2014), and base our interpretation on this.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main result.

1. For RCTs we will only include studies with a low risk of bias for selection bias and attrition. For the NRSIs we will do a sensitivity analysis looking at the studies deemed to be at an overall low to moderate risk of bias by the ROBINS-I tool excluding those judged as serious and critical.
2. We will carry out a sensitivity analysis on the inclusion of unadjusted data versus adjusted data
3. We will carry out a sensitivity analysis on the impact on missing data but excluding studies judged at high risk for missing data
4. We will carry out a sensitivity analysis for NRSIs looking at different study design features (if pooled).

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.

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APPENDICES

Appendix 1. Summary of constituents of prothrombin complex concentrate

Name	FII	FVII	FIX	FX	Protein C/S	Additive
Beriplex[a]	111	57	100	150	Yes	Heparin, AT
Octaplex[a]	98	66	100	96	Yes	Heparin
Bebulin[a]	120	13	100	139	No	Heparin
Profilnine[a]	148	11	100	64	No	No heparin
Cofact[a]	106	48	100	103	Yes	No heparin
Prothrombinex[b]	100	-	100	100	No	Heparin, AT

AT: antithrombin; **FII:** coagulation factor two; **FVII:** coagulation factor seven; **FIX:** coagulation factor nine; **FX:** coagulation factor ten.

[a]Ghadimi 2016
[b]Product Information - Prothrombinex-VF

Appendix 2. Preliminary MEDLINE (Ovid) search strategy

1 Factor IX/ (5009)

2 prothrombin complex concentrate.tw. (1032)

3 pcc*.tw. (13414)

4 factor IX.tw. (4006)

5 beriplex.tw. (52)

6 octaplex.tw. (36)

7 bebulin.tw. (12)

8 profilnine.tw. (18)

9 cofact.tw. (8)

10 prothrombinex.tw. (22)

11 kcentra.tw. (29)

12 confidex.tw. (6)

13 kaskadil.tw. (3)

14 kedcom.tw. (0)

15 ocplex.tw. (0)

16 pronativ.tw. (0)

17 prothromplex.tw. (17)

18 PPSB.tw. (116)

19 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (20441)

20 Thoracic Surgery/ (12536)

21 exp Cardiovascular Surgical Procedures/ (382026)

22 ((cardio* or cardiac* or heart) adj3 surg*).tw. (75347)

23 ((cardio* or cardiac* or heart or coronary) adj3 surg*).tw. (90877)

24 (non-surgical adj3 bleed*).tw. (73)

25 Coagulopathy.tw. (12478)

26 20 or 21 or 22 or 23 or 24 or 25 (437947)

27 19 and 26 (535)

28 limit 27 to yr="2000-current" (451)

CONTRIBUTIONS OF AUTHORS

KH - drafting the protocol

MF - drafting the protocol

LY - drafting the protocol

VJ - drafting the protocol

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LY - conference costs for a pharmaceutical company unrelated to the topic of interest; payment from the manufacturer of Prothrombinex in Australasia for involvement in a clinical trial unrelated to Prothrombinex

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